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Movement Disorders Journal (Article)

Bilateral subthalamic stimulation improves aspects of non-motor symptoms in Parkinson's disease

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Abbreviations:

6 months follow-up (6MFU)

Activities of daily living (ADL)

Deep brain stimulation (DBS)

Levodopa equivalent daily dose (LEDD)

Non-motor symptoms (NMS)

NMS Scale (NMSS)

NMS Questionnaire (NMSQ)

Parkinson’s disease (PD)

PD Questionnaire (PDQ)

Quality of life (QoL)

Short Parkinson's Evaluation Scale/Scales for Outcomes in Parkinson's disease
(SPES/SCOPA)

Subthalamic nucleus (STN)

Unified Parkinson's Disease Rating Scale (UPDRS)

Abstract

BACKGROUND

STN-DBS is well established to improve motor symptoms and quality of life in patients with PD. While non-motor symptoms are crucial for quality of life in these patients, only neuropsychiatric and neuropsychological symptoms have been systematically studied in a longitudinal design thus far. However, these are only a part of the spectrum of non-motor symptoms in PD. We hypothesized that STN-DBS is associated with a beneficial effect on a range of non-motor symptoms.

METHODS

In this multicenter, open, prospective, international study we investigated non-motor effects of STN-DBS in “real-life” use. We evaluated Non-motor Symptom Scale, and Questionnaire, PD Questionnaire-8, Scales for Outcomes of PD motor examination and complications, and activities of daily living preoperatively and at 6 months follow-up in 60 consecutive patients (35 male, mean age: 61.64 ± 7.84 years, mean disease duration: 10.45 ± 4.22 years) undergoing STN-DBS.

RESULTS

All outcomes improved significantly at 6 months follow-up (PD Questionnaire-8, $p=0.006$; activities of daily living, $p=0.012$; all others, $p<0.001$; Wilcoxon signed-rank, respectively paired t-test; Bonferroni-correction). Post-hoc analyses of Non-motor Symptom Scale domains showed a significant reduction of sleep/fatigue and miscellaneous domains ($p\leq 0.001$), perceptual problems/hallucinations ($p=0.036$), and urinary ($p=0.018$) scores. Effect sizes were “moderate” effect for Non-motor

Symptom Scale, and motor complications, “large” for motor examination, and “small” for other outcomes.

CONCLUSIONS

This study provides first evidence that bilateral STN-DBS improves non-motor burden in patients with PD and opens the door to a more balanced evaluation of DBS outcomes. Further randomized studies are needed to confirm these findings and compare DBS non-motor effects to other therapies such as infusion based treatments of advanced PD.

1 Introduction

Subthalamic nucleus (STN) deep brain stimulation (DBS) is well established for the symptomatic treatment of Parkinson’s disease (PD) improving motor symptoms, activities of daily living (ADL), and quality of life (QoL) ¹⁻³. Non-motor symptoms (NMS) play a crucial role for QoL in patients with PD ^{4, 5}. Long-term effects of DBS on neuropsychological ^{6, 7} and neuropsychiatric symptoms ^{8, 9} have been studied. However, these symptoms contribute only to a part of NMS in patients with PD. Previously published studies on a wider range of NMS have methodological limitations due to a lack of objective clinician-based ¹⁰ or patient-based assessment ¹¹ and small cohort sizes of only 10 subjects ^{12, 13}.

In this study, we therefore investigated prospective data using validated non-motor clinician-based and self-assessment outcome measures collected on 6 months follow-up (6MFU) of a multicenter advanced therapies registry trial. Datasets from this registry has been recently analysed to publish the EuroInf study comparing apomorphine with intrajejunal levodopa infusion. We hypothesized that STN-DBS is associated with a reduction of NMS burden in patients with PD.

Furthermore, to investigate the relationship between changes of NMS, motor and QoL outcomes from baseline, an exploratory aim of our study was to analyse their correlation.

2 Methods

2.1 Design

This was a multicenter, open, prospective, European registry study (Cologne, London, and Manchester) of a subgroup of the “Non Motor Symptoms study group” of the “International Parkinson’s disease and Movement Disorders Society” with a longitudinal follow-up (EuroInf study). The “Non Motor Symptoms study group” has previously published results of two other arms of the EuroInf study (subcutaneous apomorphine and intrajejunal levodopa infusion therapies)¹⁴.

For the third arm, centers were chosen on the basis of experience in using motor and non-motor scales as well as performing DBS surgery and therapy.

2.2 Subjects

All patients were diagnosed according to British Brain Bank criteria¹⁵ and were screened for treatment with DBS in accordance with consensus criteria of the International Parkinson’s disease and Movement Disorders Society due to an insufficient medical control of motor symptoms. All patients responded to levodopa with >30% improvement of motor symptoms, assessed by Unified Parkinson’s Disease Rating Scale (UPDRS)-III. Preoperatively, neuropsychiatric and neuropsychological assessments of patients were performed by consultant psychiatrists and neuropsychologists. Exclusion criteria were clinically significant

psychiatric diseases and Minimal Mental State Examination scores < 25 points as an indicator of neuropsychological impairment.

2.3 Ethical approval

The study was approved by the local ethics committees (Master vote: 12–145, Cologne; United Kingdom: National Research Ethics Service South East London REC 3; 10/H0808/141; NIHR portfolio (UKCRN) number 10084) and carried out in accordance with the Declaration of Helsinki.

2.4 Clinical assessment

Motor symptoms and NMS were assessed preoperatively in clinical MedON state and postoperatively on 6MFU in clinical MedON/StimON before an adjustment of stimulation parameters thus reflecting a “real-life” state. As part of the EuroInf study, the same scales were collected as reported previously for other invasive symptomatic therapies of PD (apomorphine- and intrajejunal levodopa-infusion therapy) ^{14, 16, 17}.

(A) Motor impairment was assessed with the Short Parkinson’s Evaluation Scale / Scales for Outcomes in Parkinson’s disease (SPES/SCOPA) motor examination which has been shown to highly correlate with the MDS-UPDRS motor examination ¹⁸. Motor complications and ADL were also assessed with the SPES/SCOPA scale which correlates with corresponding parts of the UPDRS scale ¹⁹. Additionally, for a subset of patients, we examined UPDRS directly.

(B) Non-motor symptoms were examined with two tests:

(1) We collected data of the Non-Motor Symptom Scale (NMSS), a clinician-administered scale which tests for nine domains of NMS with 30 questions ²⁰. These questions are assessed with weighted scores of symptom severity and frequency. Severity of symptoms are rated by a range of 0 (none) to 3 points (major source of

distress and disturbance for patients) and frequency is assessed by a range of 1 (<once per week) to 4 (daily or all the time) points. The theoretically possible maximum NMSS total score is 360, the minimum score 0.

(2) Furthermore, we also collected data of the Non-Motor Symptoms Questionnaire (NMSQ), a patient-based self-assessment questionnaire with dichotomous answers for the presence of NMS ²¹ with a maximum NMSQ total score of 30 corresponding to the number of questions.

(C) Patients' QoL was investigated with the self-assessment rating scale Parkinson's Disease Questionnaire (PDQ) -8 ²². The PDQ-8 was designed as a shortened version of the PDQ-39, quantifies the frequency of eight aspects of daily living with impact on the QoL, and has previously been deployed for the assessment of patients with invasive symptomatic therapies of PD ^{14, 16, 17}, including STN-DBS ²³. PDQ data is provided as PDQ-8 Summary Index ²⁴.

(D) In addition, we recorded the therapeutic medical regimen and stimulation parameters. The levodopa equivalent daily dose (LEDD) was computed according to a method previously published by Tomlinson et al. ²⁵ and the total electric energy delivered was estimated according to a method previously published by Koss et al. ²⁶.

2.3 Statistical analysis

All outcome parameters were checked for normality distribution with the Shapiro-Wilk test or, when necessary, Kolmogorov-Smirnov test with Lilliefors correction. For longitudinal analyses of these parameters we computed Wilcoxon signed-rank test, respectively Student's paired t-test when criteria for parametric tests were fulfilled. We used the Bonferroni method to correct Type I errors for multiple comparisons. All values are stated as mean \pm SD, when the aforementioned criteria were fulfilled, unless stated otherwise.

To investigate the size of DBS effects, in addition to the difference between baseline and follow-up scores, the relative change $[(\text{mean Test}_{\text{baseline}} - \text{mean Test}_{6\text{MFU}}) / \text{mean Test}_{\text{baseline}}]$ and the Cohen's effect size ²⁷ were calculated. Effect size values ≥ 0.80 are considered "large effect", 0.50-0.79 "moderate effect", and 0.20-0.49 "small effect" ²⁸. We used half a SD at baseline ($\frac{1}{2}\text{SD Test}_{\text{Baseline}}$) in a method previously applied to QoL outcomes to detect treatment responders ²⁸. The number needed to treat for an improvement $\geq \frac{1}{2}\text{SD Test}_{\text{Baseline}}$ was calculated for each outcome ²⁹. Also, to evaluate changes of specific aspects of NMS, we used post-hoc analyses of NMSS domain scores with the above mentioned methods.

Furthermore, to investigate the relationship between all outcome parameters, we computed Spearman's rho, respectively Pearson's correlation analyses when criteria were fulfilled, for changes of values from baseline. To examine the relative importance of specific NMSS domains for QoL, we also calculated correlations between all domains and PDQ-8 Summary Index. These relationships are also reported as changes from baseline.

3 Results

Here we present data of 60 consecutive patients (35 male) aged 61.64 years (± 7.84) with long histories of PD (10.45 ± 4.22 years) and moderate to high LEDD (1073.55 ± 475.93) at baseline. The median Hoehn & Yahr score was 2.75 (interquartile range: 2-3).

The assumption of normal distribution was violated for PDQ-8 Summary Index ($p=0.015$), and SPES/SCOPA motor examination ($p=0.019$), ADL ($p=0.006$) and motor complications scores ($p=0.006$), but not for NMSS total score ($p=0.066$), and NMSQ total score ($p=0.200$).

Bilateral STN-DBS in patients with PD significantly improved all outcome parameters applied in this study (see table 1). In particular, DBS significantly reduced NMS in the clinician-based NMSS total score ($p<0.001$) as well as in the patient-based NMSQ total score ($p<0.001$). Using NMSS total score as a main outcome parameter the statistical power was 0.88 ($\alpha=0.05$; two-sided test).

Post-hoc analyses of NMSS domains, also reported in table 1, showed a significant reduction of sleep/fatigue ($p<0.001$), perceptual problems/hallucinations ($p=0.036$), urinary symptoms ($p=0.018$), and miscellaneous domain ($p=0.001$) scores. An illustration of NMSS domain scores is included in figure 1.

In the latter domain questions regarding excessive sweating ($p<0.001$) and change in the ability to smell and taste ($p=0.001$) were significant. Additionally, trends were observed for cardiovascular ($p=0.096$) and gastrointestinal ($p=0.082$) symptoms. Furthermore, PDQ-8 Summary Index ($p=0.006$), ADL ($p=0.012$), and motor outcomes (motor examination and complications, $p<0.001$ respectively) improved significantly.

The magnitude of improvement is indicated in table 2. DBS had a moderate effect size on NMSS total score (0.50) and SPES/SCOPA motor complications (0.66), a large effect size on SPES/SCOPA motor examination (0.81), and a small effect size on NMSQ total score (0.48), PDQ-8 Summary Index (0.47), and SPES/SCOPA ADL (0.43). Mean of all stated outcome parameters was -29.50% (± 7.16). The mean effects size of all stated outcome parameters was 0.57 (± 0.14) resulting in a number needed to treat of 2.12 (± 0.24). Around 47% of patients treated with DBS improved ($\geq \frac{1}{2}SD_{Test_{Baseline}}$ or more) their QoL and around 42% improved NMS as indicated by the number needed to treat values.

UPDRS-III and -IV were available for a subset of patients (n=42 and n=43) and improved significantly on 6MFU (see table e-1) with large effect size (0.90 and 0.91) resulting in a number needed to treat of 1.62 and 1.60, respectively (see table e-2).

LEDD reduction was 43.22% from 1073.55 (± 475.93) to 609.59 (± 337.25) and reached statistical significance (Student's paired t-test: $p < 0.001$). Mean total electric energy delivered was 88.51 μJ (± 83.78) at 6MFU. There was no significant inter-hemispheric difference as the median and inter-quartile range of the right STN were 36.30 μJ and 19.97-68.80 μJ and of the left STN were 63.47 μJ and 16.38-84.94 μJ (Wilcoxon signed-rank test: $p = 0.904$).

To explore the relationship between changes of outcome parameters from baseline to 6MFU we computed correlation analyses (table 3) which showed a significant relationship between the improvements of NMSS total score and PDQ-8 Summary Index ($p = 0.001$) as well as NMSQ total score ($p = 0.026$). Interestingly, however, the reduction of NMSS total score was not significantly correlated to SPES/SCOPA motor examination and complications or ADL scores. The correlation analyses on the aforementioned subset of patients for which UPDRS data was available showed a significant relationship between the improvements of NMSS total score with UPDRS-IV ($p = 0.012$), but not with UPDRS-III (table e-3).

Further correlation analyses between PDQ-8 Summary Index and NMSS domains (table 4) indicated a significant relationship with sleep/fatigue ($p = 0.016$), mood/cognition ($p < 0.001$), and attention/memory ($p = 0.001$). Noteworthy, there was no correlation between PDQ-8 Summary Index and improvements of urinary and the miscellaneous NMSS domains in our cohort, although these domains significantly improved from baseline.

During the study period, no significant adverse effects were observed.

4 Discussion

This multicenter open label European study provides evidence that bilateral STN-DBS improves NMS burden in patients with PD as has been suggested from some single center studies in small cohorts.. Also, in accordance to previous studies investigating changes from baseline to 6MFU, in our cohort STN-DBS significantly improved motor outcomes and QoL ^{1, 30}. Studies investigating changes of motor examination from baseline MedON to 6MFU MedON/StimON report comparable results for motor examination improvement ^{31, 32}.

Incorporating good clinical practice we assessed NMS, QoL and motor symptoms using validated scales in a multicenter approach for the first time. Our main observations indicate that continuous bilateral subthalamic DBS significantly improves NMS, in particular its following aspects:

- Sleep/fatigue: Our results of a significant improvement of this domain are in accordance with previous studies reporting subjective and objective improvements of sleep efficiency, quality, and architecture after continuous bilateral STN-DBS ^{33, 34}.
- Urinary symptoms: Previous studies have reported immediate effects of STN-DBS on bladder control ³⁵, most likely mediated through a modulation of information transfer between the periaqueductal grey area and the cortex ³⁶. To our knowledge this is the first report of long-term effects of STN-DBS on urinary symptoms.
- Perceptual problems/hallucinations: Our results are in line with previous studies which have shown that DBS may lead to an improvement of hallucinations in patients with PD ³⁷. Although no correlations were found between LEDD reduction and an improvement of this NMSS domain (data not shown), a possible mechanism seems to be an amelioration of these symptoms depending on a

reduction of LEDD below patient-specific individual thresholds. Further studies are needed to investigate the relationship between STN-DBS and LEDD effects on perceptual problems and hallucinations.

- In the miscellaneous domain: We found beneficial effects on olfactory symptoms and excessive sweating. While previous studies have shown a beneficial immediate ³⁸ and long-term effect ³⁹ of STN-DBS on sweating probably due to a reduction of ON/OFF fluctuations, the effect on olfactory symptoms may seem more surprising. However, a longitudinal study investigating STN-DBS effects on olfaction showed a significant improvement of odor identification thresholds, but not detection thresholds, on 6 and 12MFU ⁴⁰, possibly indicating an improvement of cognitive odor information processing. Our results support these previous findings suggesting that STN-DBS may have a beneficial effect on olfaction.

Additionally trends were observed for a beneficial effect of STN-DBS on the following aspects of NMS:

- Cardiovascular symptoms: Previous studies have shown an immediate improving effect of STN-DBS on orthostatic regulation ⁴¹. In a study on immediate effects of STN-DBS on a range of NMS the severity of “dizziness” improved in the StimON-state ³⁸. To our knowledge no longitudinal data of this kind have been published. The trend of improvement of cardiovascular symptoms observed in our study could indicate long-term effects of STN-DBS on cardiovascular symptoms; however, further studies are needed.

- Gastrointestinal symptoms: A study by Arai and co-workers provided evidence for a long-term improvement of gastrointestinal dysfunction after STN-DBS ⁴². The observed trend of improvement of gastrointestinal symptoms in our study may support the aforementioned findings.

Also, a meta-analysis by Stowe and colleagues has shown an improvement of a range of NMS, including hallucinations, cardiovascular, gastrointestinal, and sleep and fatigue symptoms associated with a reduction of LEDD⁴³. The observed improvements of aforementioned aspects of NMS may therefore also reflect an indirect response to an LEDD reduction. However, DBS and LEDD reduction may also simultaneously exert effects, synergistic or competing, on NMS. A separation of these two seems difficult in a “real-life study”. Here we merely present data of “net outcome” of STN-DBS and LEDD change following DBS therapy initiation. The key findings of the current study is a beneficial overall effect of DBS initiation on QoL, motor symptoms and NMS. Further studies may help to further elucidate the interplay of effects and the weight of the individual components.

Understanding this issue may also help to answer a closely connected question, as to how STN-DBS effects on NMS as a whole can be explained, when LEDD reduction is not responsible. One has to acknowledge that NMS is a conglomeration, and classification of NMS in PD suggests multifactorial origin)Todorova et al. *Pract Neurol* 2014. Todorova A, Jenner P, Ray Chaudhuri K. Non-motor Parkinson's: integral to motor parkinson's, yet often neglected. *Practical Neurology*.2014 doi:10.1136/practneurol-2013-000741

). Most importantly 2 key aspects of NMS include dopaminergic versus non dopaminergic symptoms as well as non motor fluctuations. From a pathophysiological point of view DBS of the STN may help some NMS such as mood, aspects of sleep dysfunction and dysautonomia by modulating the dopaminergic pathways as well as by reducing motor fluctuations and thereby by default, attenuating non motor fluctuations. in theory, at least two ways of action of DBS seem possible here:

Discuss non motor fluctuations as this is a key effect (Storch et al *Neurology* 2013)

Firstly, a direct modulation of basal ganglia-thalamo-cortical loops has been discussed by which, e.g., autonomic centers of the thalamus, lateral frontal, and anterior cingulate cortex could be modulated thus leading to improvements of symptoms like sweating and bladder control^{36, 39}.

Secondly, a spread of electric current to regions in proximity of the STN, by which, e.g., the PPN (pedunculopontine nucleus) could be modulated thus, e.g., resulting in an improvement of sleep architecture ⁴⁴.

How about the roles of sensorimotor, limbic and associative STN and its frontal connections and electrode placement.

An interesting finding of the current study is that the improvement of NMSS total score was significantly correlated with the improvements of QoL (PDQ-8 Summary Index) and motor complications (UPDRS-IV) while the correlation between PDQ-8 Summary Index and motor examination (SCOPA/SPES motor examination and UPDRS-III) did not reach statistical significance. This confirms previous studies that NMSS total score may be a greater determinant of QoL than motor impairment ⁴.

As a “real-life study” the current work has a number of weaknesses and as such recommendations cannot be made on the basis of this study. As a registry study this was not a randomized or placebo-controlled study with sham stimulation. Patients were selected and recruited in a consecutive fashion as per clinical routine and underwent a standard protocol for DBS initiation in accordance to published international selection criteria for DBS as well as standard agreed follow-up plans. Patient support provided by DBS companies (e.g. an introductory training to patient programming and recharging devices) was not systematically assessed in this study, but support was available for all patients in participating study centers. However, the multicenter set-up of the study is likely to ameliorate the bias caused by a single center design and the real life designs has strong external validity. Furthermore, our study of non-motor effects of STN-DBS, as an invasive symptomatic therapeutic option, has one of the largest patient numbers for studies of this kind and it is unlikely that a sham controlled study of this nature can be performed both for logistic and financial reasons.

However, using clustering and stratification methods in cohorts with further extended patient numbers may allow a characterization of treatment responses of specific NMS subtypes⁴⁵. The aim of this process is to tailor individual therapeutic approaches for patients with PD based on their profile of NMS and motor symptoms.

To conclude, STN-DBS ameliorates NMS burden in a range of aspects of NMS. In our cohort around 40% of patients treated with DBS improved their NMS. Number needed to treat results were consistent with relative change and effect size results for all outcome parameters. Reports of these parameters are needed to better understand responses to different treatment strategies like, e.g., DBS, conventional pharmacotherapy, and subcutaneous apomorphine and intra-jejunal levodopa infusion therapies. Further studies on treatment responses of specific NMS subtypes to different treatment strategies may help to eventually provide a basis for individualized medicine for patients' "real-life requirements".

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Table 1 - Significant improvement of all outcomes.

	Baseline		Follow-Up		p
	Mean	SD	Mean	SD	
NMSS total score	65.05	39.03	45.35	25.88	<0.001
NMSS domains					
Cardiovascular	1.60	2.26	1.02	1.70	0.096
Sleep/fatigue *	17.37	10.18	9.78	7.53	<0.001
Mood/cognition	6.98	11.77	5.93	11.41	0.585
Perceptual problems / hallucinations *	1.73	3.59	0.90	2.67	0.036
Attention/memory	5.37	6.70	4.45	5.29	0.223
Gastrointestinal	6.95	7.89	5.33	5.81	0.082
Urinary *	10.73	9.81	7.83	7.55	0.018
Sexual function	3.00	5.09	2.73	5.33	0.637
Miscellaneous *	11.32	9.85	7.37	5.76	0.001
NMSQ total score	10.76	4.90	8.42	4.35	<0.001
PDQ-8 Summary Index	33.23	17.96	24.74	16.00	0.006
SPES/SCOPA					
motor examination	14.32	5.53	9.83	5.11	<0.001
ADL	7.57	5.87	5.87	2.91	0.001
motor complications	4.96	3.20	2.85	2.62	<0.001

* Post-hoc analyses of NMSS domains showed a significant improvement of these domains.

Table 2 – Relative change, effect size and number needed to treat

	Relative change (%)	Effect size	Number needed to treat
NMSS total score *	-30.28	0.50	2.4
NMSS domains			
Cardiovascular	-36.46	0.26	4.29
Sleep/fatigue *	-43.67	0.74	1.94
Mood/cognition	-15.04	0.09	6.00
Perceptual problems / hallucinations	-48.08	0.23	7.50
Attention/memory	-17.08	0.14	4.62
Gastrointestinal	-23.26	0.21	3.53
Urinary	-27.02	0.30	3.34
Sexual function	-8.89	0.05	7.5
Miscellaneous	-34.9	0.40	2.61
NMSQ total score	-21.73	0.48	2.11
PDQ-8 Summary Index	-25.55	0.47	2.15
SPES/SCOPA			
motor examination **	-31.00	0.81	1.82
ADL	-22.49	0.43	2.35
motor complications *	-42.54	0.66	1.87

* „Moderate“ effect size

** „Strong“ effects size

Table 3 – Spearman's rank correlations between outcomes

		NMSS total score	NMSQ total score	PDQ-8 Summary Index	SPES / SCOPA motor examination	SPES / SCOPA ADL
NMSQ total score	Correlation	.290*				
	Sig. (2- tailed)	.026				
	N	59				
PDQ-8 Summary Index	Correlation	.428**	.371**			
	Sig. (2- tailed)	.001	.004			
	N	60	59			
SPES / SCOPA motor examination	Correlation	.174	.127	.293*		
	Sig. (2- tailed)	.184	.339	.023		
	N	60	59	60		
SPES / SCOPA ADL	Correlation	.253	.000	.398**	.311*	
	Sig. (2- tailed)	.065	1.000	.003	.022	
	N	54	53	54	54	
SPES / SCOPA motor complications	Correlation	.201	.052	-.022	-.099	.168
	Sig. (2- tailed)	.144	.714	.874	.477	.224
	N	54	53	54	54	54

** Correlation is significant at the 0.01 level (2-tailed).

* Correlation is significant at the 0.05 level (2-tailed).

There were no missing data for NMSS total score, PDQ-8 Summary Index, and SPES/SCOPA motor examination. Missing data for SPES/SCOPA ADL and motor complications were acceptable and for NMSQ total score negligible.

Table 4 – Correlations between PDQ-8 Summary Index and NMSS domains

		Cardio-vascular	Sleep / fatigue	Mood / cognition	Perceptual problems / hallucinations	Attention / memory	Gastro-intestinal	Urinary	Sexual function	Miscellaneous
PDQ-8	Correlation	.129	.311*	.496**	.199	.410**	.127	.138	-.109	.180
Summary	Sig. (2-tailed)	.327	.016	.000	.128	.001	.333	.292	.406	.168
Index	N	60	60	60	60	60	60	60	60	60

* Correlation is significant at the 0.05 level (2-tailed).

** Correlation is significant at the 0.01 level (2-tailed).

There were no missing data for PDQ-8 Summary Index and NMSS domains.

Legend to figure 1

(a) Box plots and (b) radar chart of NMSS domains. Star marks significantly improved domains. (B) Domain scores normalized to baseline values per subject. Blue: baseline, copper: 6MFU. Bigger copper area reflects NMSS domain improvement (computation: $2 - 6\text{MFU}/\text{baseline}$).